

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

# SEARCH REQUEST FORM

Requestor's Name: \_\_\_\_\_ Serial Number: \_\_\_\_\_  
Date: \_\_\_\_\_ Phone: \_\_\_\_\_ Art Unit: \_\_\_\_\_

## Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

BEST AVAILABLE COPY

## STAFF USE ONLY

Date completed: <u>12/23</u>	Search Site: _____	Vendors: _____
Searcher: <u>P. Schreiber 308-4292</u>	<input type="checkbox"/> STIC	<input type="checkbox"/> IG
Terminal time: <u>7</u>	<input checked="" type="checkbox"/> CM-1 <u>6A03</u>	<input type="checkbox"/> STN
Elapsed time: <u>11</u>	<input type="checkbox"/> Pre-S	<input type="checkbox"/> Dialog
CPU time: _____	Type of Search: _____	<input type="checkbox"/> APS
Total time: _____	<input type="checkbox"/> N.A. Sequence	<input type="checkbox"/> Geninfo
Number of Searches: _____	<u>2</u> <input type="checkbox"/> A.A. Sequence	<input type="checkbox"/> SDC
Number of Databases: _____	<input type="checkbox"/> Structure	<input type="checkbox"/> DARC/Questel
	<input type="checkbox"/> Bibliographic	<input checked="" type="checkbox"/> Other <u>omig 50</u>

FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002

=> file medline

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		0.21	0.21

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

FILE LAST UPDATED: 19 DEC 2002 (20021219/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/summ2003.html> for a description on changes.

If you received SDI results from MEDLINE on October 8, 2002, these may have included old POPLINE data and in some cases duplicate abstracts. For further information on this situation, please visit NLM at: [http://www.nlm.nih.gov/pubs/techbull/so02/so02\\_popline.html](http://www.nlm.nih.gov/pubs/techbull/so02/so02_popline.html)

To correct this problem, CAS will remove the POPLINE records from the MEDLINE file and process the SDI run dated October 8, 2002 again.

Customers who received SDI results via email or hard copy prints on October 8, 2002 will not be charged for this SDI run. If you received your update online and displayed answers, you may request a credit by contacting the CAS Help Desk at 1-800-848-6533 in North America or 614-447-3698 worldwide, or via email to [help@cas.org](mailto:help@cas.org)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s insulin

L1 195067 INSULIN

=> s l1 and a16 and a17

199 A16

134 A17

L2 2 L1 AND A16 AND A17

=> d 1-2

L2 ANSWER 1 OF 2 MEDLINE

AN 2000485734 MEDLINE

DN 20487207 PubMed ID: 11034394

TI Alanine scanning mutants of rat proinsulin I show functional diversity of anti-insulin monoclonal antibodies.

AU Tikhomirov O Y; Thomas J W

CS Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232, USA.

NC DK43911 (NIDDK)

P30CA68485 (NCI)

SO JOURNAL OF IMMUNOLOGY, (2000 Oct 1) 165 (7) 3876-82.

Journal code: 2985117R. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200011

ED Entered STN: 20010322

Last Updated on STN: 20010322

Entered Medline: 20001103

L2 ANSWER 2 OF 2 MEDLINE

AN 97294699 MEDLINE

DN 97294699 PubMed ID: 9148904

TI Alanine scanning mutagenesis of insulin.

AU Kristensen C; Kjeldsen T; Wiberg F C; Schaffer L; Hach M; Havelund S; Bass

J; Steiner D F; Andersen A S

CS Department of Insulin Research, Novo Nordisk, 2880 Bagsvaerd, Denmark.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 16) 272 (20) 12978-83.

Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199706

ED Entered STN: 19970630

Last Updated on STN: 19970630

Entered Medline: 19970619

=> d 2 kwic

L2 ANSWER 2 OF 2 MEDLINE

TI Alanine scanning mutagenesis of insulin.

AB Alanine scanning mutagenesis has been used to identify specific side chains of insulin which strongly influence binding to the insulin receptor. A total of 21 new insulin analog

constructs were made, and in addition 7 high pressure liquid chromatography-purified analogs were tested, covering alanine substitutions in positions. . . B8, B9, B10, B11, B12, B13, B16, B17, B18, B20, B21, B22, B26, A4, A8, A9, A12, A13, A14, A15, A16, A17, A19, and A21. Binding data on the analogs revealed that the alanine mutations that were most disruptive for binding were. . .

TyrA19, GlyB8, LeuB11, and GluB13, resulting in decreases in affinity of 1,000-, 33-, 14-, and 8-fold, respectively, relative to wild-type insulin. In contrast, alanine substitutions at positions GlyB20, ArgB22, and SerA9 resulted in an increase in affinity for the insulin receptor. The most striking finding is that B20Ala insulin retains high affinity binding to the receptor. GlyB20 is conserved in insulins from different species, and in the structure of. . . likely modifies the structure of the B-chain in this region, but this structural change appears to enhance binding to the insulin receptor.

CT Check Tags: Animal; Human

\*Alanine: GE, genetics

Amino Acid Sequence

\*Insulin: GE, genetics

Molecular Sequence Data

Mutagenesis, Site-Directed

\*Mutation

RN 11061-68-0 (Insulin); 56-41-7 (Alanine)

=> d his

(FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002)

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

L1 195067 S INSULIN

L2 2 S L1 AND A16 AND A17

=> s l1 and B7

4761 B7

L3 153 L1 AND B7

=> s l3 and a7

716 A7

L4 15 L3 AND A7

=> d 1-15

L4 ANSWER 1 OF 15 MEDLINE

AN 2002713196 IN-PROCESS

DN 22363230 PubMed ID: 12475219

TI A protein caught in a kinetic trap: structures and stabilities of insulin disulfide isomers.

AU Hua Qing-Xin; Jia Wenhua; Frank Bruce H; Phillips Nelson F B; Weiss Michael A

CS Department of Biochemistry, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, Ohio 44106, and Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285.

SO BIOCHEMISTRY, (2002 Dec 17) 41 (50) 14700-15.

Journal code: 0370623. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS IN-PROCESS; NONINDEXED; Priority Journals

ED Entered STN: 20021217

Last Updated on STN: 20021217

L4 ANSWER 2 OF 15 MEDLINE

AN 2002009747 MEDLINE

DN 21245116 PubMed ID: 11347892

TI Effects of cysteine to serine substitutions in the two inter-chain disulfide bonds of insulin.

AU Guo Z Y; Feng Y M

CS State Key Laboratory of Molecular Biology, Shanghai Institute of Biochemistry, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, People's Republic of China.

SO BIOLOGICAL CHEMISTRY, (2001 Mar) 382 (3) 443-8.  
Journal code: 9700112. ISSN: 1431-6730.

CY Germany: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200112

ED Entered STN: 20020121

Last Updated on STN: 20020121

Entered Medline: 20011204

L4 ANSWER 3 OF 15 MEDLINE

AN 2001559177 MEDLINE

DN 21475289 PubMed ID: 11591149

TI Hierarchical protein folding: asymmetric unfolding of an insulin analogue lacking the A7-B7 interchain disulfide bridge.

AU Hua Q X; Nakagawa S H; Jia W; Hu S Q; Chu Y C; Katsoyannis P G; Weiss M A

CS Department of Biochemistry, Case Western Reserve University School of Medicine, Cleveland, Ohio 44016, USA.

SO BIOCHEMISTRY, (2001 Oct 16) 40 (41) 12299-311.  
Journal code: 0370623. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200111

ED Entered STN: 20011022

Last Updated on STN: 20011105

Entered Medline: 20011101

L4 ANSWER 4 OF 15 MEDLINE

AN 2001159971 MEDLINE

DN 21159059 PubMed ID: 11258877

TI Putative disulfide-forming pathway of porcine insulin precursor during its refolding in vitro.

AU Qiao Z S; Guo Z Y; Feng Y M

CS State Key Laboratory of Molecular Biology, Shanghai Institute of Biochemistry, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yue-Yang Road, Shanghai 200031, People's Republic of China.

SO BIOCHEMISTRY, (2001 Mar 6) 40 (9) 2662-8.  
Journal code: 0370623. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200105

ED Entered STN: 20010517

Last Updated on STN: 20010517

Entered Medline: 20010510

L4 ANSWER 5 OF 15 MEDLINE

AN 97436781 MEDLINE

DN 97436781 PubMed ID: 9291463

TI Expression of homeobox genes, including an insulin promoting factor, in the murine yolk sac at the time of hematopoietic initiation.

AU McGrath K E; Palis J

CS Department of Pediatrics, University of Rochester Medical Center, NY 14642, USA.

NC CA 09363C (NCI)  
R29 HL45573 (NHLBI)

SO MOLECULAR REPRODUCTION AND DEVELOPMENT, (1997 Oct) 48 (2) 145-53.

Journal code: 8903333. ISSN: 1040-452X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199712

ED Entered STN: 19980109

Last Updated on STN: 19980109

Entered Medline: 19971202

L4 ANSWER 6 OF 15 MEDLINE

AN 94186288 MEDLINE

DN 94186288 PubMed ID: 8138354

TI Direct assignment of disulfide bonds by Edman degradation of selected peptide fragments.

AU Haniu M; Acklin C; Kenney W C; Rohde M F

CS Department of Protein Structure, Amgen, Inc., Thousand Oaks, California.

SO INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1994 Jan) 43 (1) 81-6.

Journal code: 0330420. ISSN: 0367-8377.

CY Denmark

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199404

ED Entered STN: 19940509

Last Updated on STN: 20000303

Entered Medline: 19940425

L4 ANSWER 7 OF 15 MEDLINE

AN 93191924 MEDLINE

DN 93191924 PubMed ID: 1294186

TI Chemical stability of insulin. 4. Mechanisms and kinetics of chemical transformations in pharmaceutical formulation.

AU Brange J

CS Novo Research Institute, Bagsvaerd, Denmark.

SO ACTA PHARMACEUTICA NORDICA, (1992) 4 (4) 209-22.  
Journal code: 8915967. ISSN: 1100-1801.

CY Sweden

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199304

ED Entered STN: 19930423

Last Updated on STN: 19930423

Entered Medline: 19930412

L4 ANSWER 8 OF 15 MEDLINE

AN 91197423 MEDLINE

DN 91197423 PubMed ID: 2085412

TI Studies on the total synthesis of an A7,B7-dicarbainsulin. III. Assembly of segments and generation of biological activity.

AU Videnov G; Buttner K; Casaretto M; Fohles J; Gattner H G; Stoev S; Brandenburg D

CS Institute of Molecular Biology, Bulgarian Academy of Sciences, Sofia.

SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1990 Nov) 371 (11) 1057-66.

Journal code: 8503054. ISSN: 0177-3593.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199105

ED Entered STN: 19910607

Last Updated on STN: 20000303

Entered Medline: 19910520

L4 ANSWER 9 OF 15 MEDLINE

AN 90370040 MEDLINE

DN 90370040 PubMed ID: 1697643

TI Characterization of agretopes and epitopes involved in the presentation of beef insulin to T cells.

AU Fotedar A; Smart W; Boyer M; Dillon T; Fraga E; Lauzon J; Shevach E M; Singh B

CS Department of Immunology, University of Alberta, Edmonton, Canada.

SO MOLECULAR IMMUNOLOGY, (1990 Jul) 27 (7) 603-11.

Journal code: 7905289. ISSN: 0161-5890.

CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199010  
ED Entered STN: 19901109  
Last Updated on STN: 19960129  
Entered Medline: 19901011

L4 ANSWER 10 OF 15 MEDLINE  
AN 90121745 MEDLINE  
DN 90121745 PubMed ID: 2692613  
TI Synthesis of A7,B7-dicarbainulin, an analogue with a noncleavable bond between A- and B-chain. II. Synthesis of the A-chain segments.  
AU Videnov G; Stoev S; Brandenburg D  
CS Institute of Molecular Biology, Bulgarian Academy of Sciences, Sofia.  
SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1989 Oct) 370 (10) 1103-11.  
Journal code: 8503054. ISSN: 0177-3593.

CY GERMANY, WEST: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199003  
ED Entered STN: 19900328  
Last Updated on STN: 19900328  
Entered Medline: 19900308

L4 ANSWER 11 OF 15 MEDLINE  
AN 89256664 MEDLINE  
DN 89256664 PubMed ID: 2656861  
TI Processing and presentation of insulin. II. Evidence for intracellular, plasma membrane-associated and extracellular degradation of human insulin by antigen-presenting B cells.  
AU Semple J W; Ellis J; Delovitch T L  
CS Banting and Best Department of Medical Research, University of Toronto, Ontario, Canada.  
SO JOURNAL OF IMMUNOLOGY, (1989 Jun 15) 142 (12) 4184-93.  
Journal code: 2985117R. ISSN: 0022-1767.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 198907  
ED Entered STN: 19900306  
Last Updated on STN: 19900306  
Entered Medline: 19890706

L4 ANSWER 12 OF 15 MEDLINE  
AN 87099888 MEDLINE  
DN 87099888 PubMed ID: 3541902  
TI The identification of a major product of the degradation of insulin by 'insulin proteinase' (EC 3.4.22.11).  
AU Muir A; Offord R E; Davies J G  
SO BIOCHEMICAL JOURNAL, (1986 Aug 1) 237 (3) 631-7.  
Journal code: 2984726R. ISSN: 0264-6021.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 198701  
ED Entered STN: 19900302  
Last Updated on STN: 19970203  
Entered Medline: 19870128

L4 ANSWER 13 OF 15 MEDLINE  
AN 80070613 MEDLINE  
DN 80070613 PubMed ID: 511097  
TI Synthesis and biological activity of seventeen analogues of human insulin.  
AU Marki F; de Gasparo M; Eisler K; Kamber B; Riniker B; Rittel W; Sieber P  
SO HOPPE-SEYLER ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1979 Nov) 360 (11) 1619-32.  
Journal code: 2985060R. ISSN: 0018-4888.  
CY GERMANY, WEST: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)

LA English  
FS Priority Journals  
EM 198002  
ED Entered STN: 19900315  
Last Updated on STN: 19900315  
Entered Medline: 19800228

L4 ANSWER 14 OF 15 MEDLINE  
AN 78108222 MEDLINE  
DN 78108222 PubMed ID: 627397  
TI Synthesis and biological activity of two disulphide bond isomers of human insulin: [A7-A11,A6-B7-cystine]- and [A6-A7,A11-B7-cystine]insulin (human).  
AU Sieber P; Eisler K; Kamber B; Riniker B; Rittel W; Marki F; de Gasparo M  
SO HOPPE-SEYLER ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1978 Jan) 359 (1) 113-23.  
Journal code: 2985060R. ISSN: 0018-4888.  
CY GERMANY, WEST: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 197804  
ED Entered STN: 19900314  
Last Updated on STN: 19900314  
Entered Medline: 19780426

L4 ANSWER 15 OF 15 MEDLINE  
AN 75039933 MEDLINE  
DN 75039933 PubMed ID: 4803251  
TI Selective cleavage of one disulfide bond in insulin: preparation and properties of insulin A7-B7 -di-S-sulfonate.  
AU Busse W D; Gattner H G  
SO HOPPE-SEYLER ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1973 Feb) 354 (2) 147-55.  
Journal code: 2985060R. ISSN: 0018-4888.  
CY GERMANY, WEST: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 197502  
ED Entered STN: 19900310  
Last Updated on STN: 19900310  
Entered Medline: 19750203

=> d 13 abs

L4 ANSWER 13 OF 15 MEDLINE  
AB We synthesized seventeen analogues of human insulin, applying the principle of stepwise, selective formation of the disulphide bonds. Most of these analogues only differ from human insulin in the replacement of a single amino acid in positions 2, 5, 6, 7, 8 and 11 of the A chain and 5, 7, 13 and 16 of the B-chain. The influence of these modifications on the physicochemical properties of the analogues is discussed. Eight analogues could be crystallized. All the analogues produce the same biological effects as insulin, but differ markedly in their potency. In isolated fat cells in vitro, [HisA8] insulin showed a relative potency of 2.46 in stimulating glucose oxidation (human insulin = 1), whereas [D-CysA6,A11] insulin had a potency of only 0.00027. Very low potency was observed when IleA2 or the half-cystines A6, A7, A11 or B7 were modified. Replacement of the invariant GlnA5 by alanine only reduced potency slightly. All the analogues are full agonists. The effects of the analogues on glucose oxidation and lipolysis are correlated, supporting the view that they are mediated by a common receptor on the fat-cell membrane. Hypoglycaemic potencies in the rat were similar to potencies in vitro. As expected, no correlation was demonstrable between antiserum binding--measured in the radioimmunoassay--and biological activity. Several results of this investigation are difficult to reconcile with the current view regarding the structure-activity relationship of insulin which appears to require further refinement.

=> d 1 abs

## L4 ANSWER 1 OF 15 MEDLINE

AB Proinsulin contains six cysteines whose specific pairing (A6-A11, A7-B7, and A20-B19) is a defining feature of the insulin fold. Pairing information is contained within A and B domains as demonstrated by studies of insulin chain recombination. Two insulin isomers containing non-native disulfide bridges ([A7-A11,A6-B7,A20-B19] and [A6-A7,A11-B7,A20-B19]), previously prepared by directed chemical synthesis, are metastable and biologically active. Remarkably, the same two isomers are preferentially formed from native insulin or proinsulin following disulfide reassortment in guanidine hydrochloride. The absence of other disulfide isomers suggests that the observed species exhibit greater relative stability and/or kinetic accessibility. The structure of the first isomer ([A7-A11,A6-B7,A20-B19], insulin-swap) has been described [Hua, Q. X., Gozani, S. N., Chance, R. E., Hoffmann, J. A., Frank, B. H., and Weiss, M. A. (1995) Nat. Struct. Biol. 2, 129-138]. Here, we demonstrate that the second isomer (insulin-swap2) is less ordered than the first. Nativelike elements of structure are retained in the B chain, whereas the A chain is largely disordered. Thermodynamic studies of guanidine denaturation demonstrate the instability of the isomers relative to native insulin ( $\Delta\Delta G(u) > 3$  kcal/mol). In contrast, insulin-like growth factor I (IGF-I) and the corresponding isomer IGF-swap, formed as alternative products of a bifurcating folding pathway, exhibit similar cooperative unfolding transitions. The insulin isomers are similar in structure and stability to two-disulfide analogues whose partial folds provide models of oxidative folding intermediates. Each exhibits a nativelike B chain and less-ordered A chain. This general asymmetry is consistent with a hierarchical disulfide pathway in which nascent structure in the B chain provides a template for folding of the A chain. Structures of metastable disulfide isomers provide probes of the topography of an energy landscape.

=&gt; d his

(FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002)

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

L1 195067 S INSULIN  
 L2 2 S L1 AND A16 AND A17  
 L3 153 S L1 AND B7  
 L4 15 S L3 AND A7

=&gt; s l1 and b25

108 B25

L5 87 L1 AND B25

=&gt; s l5 and b26

137 B26

L6 32 L5 AND B26

=&gt; s l6 and b27

3488 B27

L7 1 L6 AND B27

=&gt; d

## L7 ANSWER 1 OF 1 MEDLINE

AN 2001133417 MEDLINE

DN 21066359 PubMed ID: 11145591

TI Identification of insulin domains important for binding to and degradation by endosomal acidic insulinase.

AU Authier F; Danielsen G M; Kouach M; Briand G; Chauvet G

CS Institut National de la Sante et de la Recherche Medicale U510 (F.A.),  
 Faculte de Pharmacie Paris XI, 92296 Chatenay-Malabry, France..  
 authier@cep.u-psud.fr

SO ENDOCRINOLOGY, (2001 Jan) 142 (1) 276-89.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200103

ED Entered STN: 20010404

Last Updated on STN: 20010404

=&gt; d abs

## L7 ANSWER 1 OF 1 MEDLINE

AB The endosomal compartment of hepatic parenchymal cells contains an acidic

endopeptidase, endosomal acidic insulinase (EAI), which hydrolyzes internalized insulin at a limited number of sites. Although the positions of these cleavages are partially known, the residues of insulin important in its binding to and proteolysis by EAI have not been defined. To this end, we have studied the degradation over time of native human insulin and three insulin-analog peptides using a soluble endosomal extract from rat liver parenchyma followed by purification of the products by HPLC and determination of their structure by mass spectrometry. We found variable rates of ligand processing, i.e. high ([Asp(B10)]- and [Glu(A13),Glu(B10)]-insulin), moderate (insulin) and low (the H2-analog). On the basis of IC(50) values, competition studies revealed that human and mutant insulins display nearly equivalent affinity for the EAI. Proteolysis of human and mutant insulins by EAI resulted in eight cleavages in the B-chain which occurred in the central region (Glu(B13)-Leu(B17)) and at the C-terminus (Arg(B22)-Thr(B27)), the latter region comprising the initial cleavages at Phe(B24)-Phe(B25) (major pathway) and Phe(B25)-Tyr(B26) (minor pathway) bonds. Except for the [Glu(A13),Glu(B10)]-insulin mutant, only one cleavage on the A-chain was observed at residues Gln(A15)-Leu(A16). Analysis of the nine cleavage sites showed a preference for hydrophobic and aromatic amino acid residues on both the carboxyl and amino sides of a cleaved peptide bond. Using the B-chain alone as a substrate resulted in a 30-fold increase in affinity for EAI and a 6-fold increase in the rate of hydrolysis compared with native insulin. A similar role for the C-terminal region of the B-chain of insulin in the high-affinity recognition of EAI was supported by the use of the corresponding B(22)-B(30) peptide, which displayed an increase in EAI affinity similar to the entire B-chain vs. wild-type insulin. Thus, we have identified a highly specific molecular interaction of insulin with EAI at the aromatic locus Phe(B24)-Phe(B25)-Tyr(B26). Analytical subfractionation of a postmitochondrial supernatant fraction showed that a pulse of internalized [(125)I]Tyr(A14)-H2-analog, a protease-resistant insulin analog, undergoes a greater lysosomal transfer and lesser degradation than [(125)I]Tyr(A14)-insulin, confirming that endosomal sorting is regulated directly or indirectly by endosomal proteolysis.

=&gt; d his

(FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002)

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

L1 195067 S INSULIN  
 L2 2 S L1 AND A16 AND A17  
 L3 153 S L1 AND B7  
 L4 15 S L3 AND A7  
 L5 87 S L1 AND B25  
 L6 32 S L5 AND B26  
 L7 1 S L6 AND B27

=&gt; s l6 and b28

148 B28

L8 0 L6 AND B28

=&gt; d l6 1-32

## L6 ANSWER 1 OF 32 MEDLINE

AN 2001133417 MEDLINE

DN 21066359 PubMed ID: 11145591

TI Identification of insulin domains important for binding to and degradation by endosomal acidic insulinase.

AU Authier F; Danielsen G M; Kouach M; Briand G; Chauvet G

CS Institut National de la Sante et de la Recherche Medicale U510 (F.A.),  
 Faculte de Pharmacie Paris XI, 92296 Chatenay-Malabry, France..  
 authier@cep.u-psud.fr

SO ENDOCRINOLOGY, (2001 Jan) 142 (1) 276-89.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 200103  
 ED Entered STN: 20010404  
 Last Updated on STN: 20010404  
 Entered Medline: 20010301

L6 ANSWER 2 OF 32 MEDLINE  
 AN 2001116726 MEDLINE  
 DN 20573576 PubMed ID: 11123908  
 TI Mutational analysis of invariant valine B12 in insulin: implications for receptor binding.  
 AU Nakagawa S H; Tager H S; Steiner D F  
 CS Department of Biochemistry and Molecular Biology, The University of Chicago, Chicago, Illinois 60637, USA.. shn2@midway.uchicago.edu  
 NC DK 18347 (NIDDK)  
 DK 20595 (NIDDK)  
 SO BIOCHEMISTRY, (2000 Dec 26) 39 (51) 15826-35.  
 Journal code: 0370623. ISSN: 0006-2960.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200102  
 ED Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010215

L6 ANSWER 3 OF 32 MEDLINE  
 AN 97157004 MEDLINE  
 DN 97157004 PubMed ID: 9003385  
 TI The characterization of endosomal insulin degradation intermediates and their sequence of production.  
 AU Seabright P J; Smith G D  
 CS University of Cambridge, Department of Clinical Biochemistry, Addenbrooke's Hospital, U.K.  
 SO BIOCHEMICAL JOURNAL, (1996 Dec 15) 320 ( Pt 3) 947-56.  
 Journal code: 2984726R. ISSN: 0264-6021.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199702  
 ED Entered STN: 19970305  
 Last Updated on STN: 20000303  
 Entered Medline: 19970214

L6 ANSWER 4 OF 32 MEDLINE  
 AN 96122171 MEDLINE  
 DN 96122171 PubMed ID: 8537175  
 TI Structure-function relationships of des-(B26-B30)-insulin.  
 AU Spoden M; Gattner H G; Zahn H; Brandenburg D  
 CS Deutsches Wollforschungsinstitut, Aachen, Germany.  
 SO INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1995 Sep-Oct) 46 (3-4) 221-7.  
 Journal code: 0330420. ISSN: 0367-8377.  
 CY Denmark  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199602  
 ED Entered STN: 19960221  
 Last Updated on STN: 20000303  
 Entered Medline: 19960208

L6 ANSWER 5 OF 32 MEDLINE  
 AN 95050741 MEDLINE  
 DN 95050741 PubMed ID: 7961885  
 TI Cross-linking of a B25 azidophenylalanine insulin derivative to the carboxyl-terminal region of the alpha-subunit of the insulin receptor. Identification of a new insulin-binding domain in the insulin receptor.  
 AU Kurose T; Pashmforoush M; Yoshimasa Y; Carroll R; Schwartz G P; Burke G T; Katsoyannis P G; Steiner D F  
 CS Department of Biochemistry and Molecular Biology, University of Chicago, Illinois 60637.  
 NC DK 12925 (NIDDK)  
 DK 13914 (NIDDK)  
 DK 20595 (NIDDK)  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Nov 18) 269 (46) 29190-7.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199412  
 ED Entered STN: 19950110  
 Last Updated on STN: 20000303  
 Entered Medline: 19941219

L6 ANSWER 6 OF 32 MEDLINE  
 AN 94280635 MEDLINE  
 DN 94280635 PubMed ID: 8011179  
 TI An insulin with the native sequence but virtually no activity.  
 AU Wollmer A; Gilge G; Brandenburg D; Gattner H G  
 CS Institut für Biochemie, Rheinisch-Westfälische Technische Hochschule Aachen, Germany.  
 SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1994 Mar) 375 (3) 219-22.  
 Journal code: 8503054. ISSN: 0177-3593.  
 CY GERMANY: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199407  
 ED Entered STN: 19940810  
 Last Updated on STN: 20000303  
 Entered Medline: 19940722

L6 ANSWER 7 OF 32 MEDLINE  
 AN 93080738 MEDLINE  
 DN 93080738 PubMed ID: 1449604  
 TI Molecular close-packing method and its application to crystal structure determination of deshexapeptide (B25-B30) insulin.  
 AU Ren Z; Liang D C  
 CS National Laboratory of Biomacromolecules, Institute of Biophysics, Academia Sinica, Beijing, PRC.  
 SO SCIENCE IN CHINA. SERIES B, CHEMISTRY, LIFE SCIENCES AND EARTH SCIENCES, (1992 Jul) 35 (7) 783-90.  
 Journal code: 8913082. ISSN: 1001-652X.  
 CY China  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199301  
 ED Entered STN: 19930129  
 Last Updated on STN: 19970203  
 Entered Medline: 19930107

L6 ANSWER 8 OF 32 MEDLINE  
 AN 93048554 MEDLINE  
 DN 93048554 PubMed ID: 1425137  
 TI Comparison of subcutaneously administered soluble insulin and des-(B26-B30)-insulin-B25-amide in rabbit, pig and healthy man.  
 AU Hartmann H; Moeser E; Creutzfeldt W  
 CS Department of Medicine, University of Göttingen, FRG.  
 SO DIABETES RESEARCH AND CLINICAL PRACTICE, (1992 Jun) 16 (3) 175-81.  
 Journal code: 8508335. ISSN: 0168-8227.  
 CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199212  
 ED Entered STN: 19930122  
 Last Updated on STN: 19970203  
 Entered Medline: 19921203

L6 ANSWER 9 OF 32 MEDLINE

AN 92104166 MEDLINE  
 DN 92104166 PubMed ID: 1761045  
 TI The solution structure of a monomeric insulin. A two-dimensional  
 1H-NMR study of des-(B26-B30)-insulin in combination  
 with distance geometry and restrained molecular dynamics.  
 AU Knegt R M; Boelens R; Ganadu M L; Kaptein R  
 CS Department of Chemistry, University of Utrecht, The Netherlands.  
 SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1991 Dec 5) 202 (2)  
 447-58.  
 Journal code: 0107600. ISSN: 0014-2956.  
 CY GERMANY: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199202  
 ED Entered STN: 19920302  
 Last Updated on STN: 19920302  
 Entered Medline: 19920211

L6 ANSWER 10 OF 32 MEDLINE  
 AN 91329405 MEDLINE  
 DN 91329405 PubMed ID: 1868095  
 TI Disposition of the phenylalanine B25 side chain during  
 insulin-receptor and insulin-insulin  
 interactions.  
 AU Mirmira R G; Tager H S  
 CS Department of Biochemistry and Molecular Biology, University of Chicago,  
 Illinois 60637.  
 NC DK18347 (NIDDK)  
 DK20595 (NIDDK)  
 GM07281 (NIGMS)  
 +  
 SO BIOCHEMISTRY, (1991 Aug 20) 30 (33) 8222-9.  
 Journal code: 0370623. ISSN: 0006-2960.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199109  
 ED Entered STN: 19911006  
 Last Updated on STN: 20000303  
 Entered Medline: 19910919

L6 ANSWER 11 OF 32 MEDLINE  
 AN 91288427 MEDLINE  
 DN 91288427 PubMed ID: 2062801  
 TI Degradation of insulin by trypsin and alpha-chymotrypsin.  
 AU Schilling R J; Mitra A K  
 CS Department of Industrial and Physical Pharmacy, School of Pharmacy and  
 Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907.  
 NC NS25284 (NINDS)  
 RR05586 (NCRR)  
 SO PHARMACEUTICAL RESEARCH, (1991 Jun) 8 (6) 721-7.  
 Journal code: 8406521. ISSN: 0724-8741.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199108  
 ED Entered STN: 19910825  
 Last Updated on STN: 19970203  
 Entered Medline: 19910806

L6 ANSWER 12 OF 32 MEDLINE  
 AN 91146803 MEDLINE  
 DN 91146803 PubMed ID: 2289630  
 TI Characterization of insulin degradation products generated in  
 liver endosomes: in vivo and in vitro studies.  
 AU Clot J P; Janicot M; Fouque F; Desbuquois B; Haumont P Y; Lederer F  
 CS Unite 30 INSERM, Hopital Necker Enfants Malades, Paris, France.  
 SO MOLECULAR AND CELLULAR ENDOCRINOLOGY, (1990 Sep 10)  
 72 (3) 175-85.  
 Journal code: 7500844. ISSN: 0303-7207.  
 CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199104

ED Entered STN: 19910419  
 Last Updated on STN: 19970203  
 Entered Medline: 19910403

L6 ANSWER 13 OF 32 MEDLINE  
 AN 91107630 MEDLINE  
 DN 91107630 PubMed ID: 1988428  
 TI Importance of the character and configuration of residues B24, B25  
 , and B26 in insulin-receptor interactions.  
 AU Mirmira R G; Nakagawa S H; Tager H S  
 CS Department of Biochemistry and Molecular Biology, University of Chicago,  
 Illinois 60637.  
 NC DK-18347 (NIDDK)  
 DK-20595 (NIDDK)  
 GM-07281 (NIGMS)  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jan 25) 266 (3)  
 1428-36.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199102  
 ED Entered STN: 19910329  
 Last Updated on STN: 20000303  
 Entered Medline: 19910227

L6 ANSWER 14 OF 32 MEDLINE  
 AN 91030925 MEDLINE  
 DN 91030925 PubMed ID: 2226126  
 TI In vivo metabolic activity of des-(B26-B30)-insulin-  
 B25-amide and related analogues in the rat.  
 AU Stumpel F; Hartmann H; Brandenburg D; Creutzfeldt W  
 CS Department of Medicine, University of Gottingen, F.R.G.  
 SO DIABETES RESEARCH AND CLINICAL PRACTICE, (1990 Jul) 9 (3)  
 257-64.  
 Journal code: 8508335. ISSN: 0168-8227.  
 CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199012  
 ED Entered STN: 19910208  
 Last Updated on STN: 19910208  
 Entered Medline: 19901204

L6 ANSWER 15 OF 32 MEDLINE  
 AN 90121745 MEDLINE  
 DN 90121745 PubMed ID: 2692613  
 TI Synthesis of A7,B7-dicarbainsulin, an analogue with a noncleavable bond  
 between A- and B-chain. II. Synthesis of the A-chain segments.  
 AU Videnov G; Stoev S; Brandenburg D  
 CS Institute of Molecular Biology, Bulgarian Academy of Sciences, Sofia.  
 SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1989 Oct) 370 (10)  
 1103-11.  
 Journal code: 8503054. ISSN: 0177-3593.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199003  
 ED Entered STN: 19900328  
 Last Updated on STN: 19900328  
 Entered Medline: 19900308

L6 ANSWER 16 OF 32 MEDLINE  
 AN 90033862 MEDLINE  
 DN 90033862 PubMed ID: 2680697  
 TI Biological activity of des-(B26-B30)-insulinamide and related  
 analogues in rat hepatocyte cultures.  
 AU Hartmann H; Oberhaus K; Spahr R; Brandenburg D; Creutzfeldt W; Probst  
 I  
 CS Department of Medicine, University of Gottingen, FRG.  
 SO DIABETOLOGIA, (1989 Jul) 32 (7) 416-20.  
 Journal code: 0006777. ISSN: 0012-186X.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English



FS Priority Journals  
EM 198912  
ED Entered STN: 19900328  
Last Updated on STN: 19980206  
Entered Medline: 19891212

L6 ANSWER 17 OF 32 MEDLINE

AN 89351014 MEDLINE

DN 89351014 PubMed ID: 2669756

TI Structure and activity of the B-chain of insulin.

AU Ng F M; Zhu S Q; Cui D F; Fan L; Huang Y D; Zhang Y S

CS Department of Biochemistry, Monash University, Melbourne, Australia.

SO BIOCHEMISTRY INTERNATIONAL, (1989 Feb) 18 (2) 373-81.

Journal code: 8100311. ISSN: 0158-5231.

CY Australia

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198909

ED Entered STN: 19900309

Last Updated on STN: 20000303

Entered Medline: 19890914

L6 ANSWER 18 OF 32 MEDLINE

AN 89274174 MEDLINE

DN 89274174 PubMed ID: 2659071

TI Drosophila insulin degrading enzyme and rat skeletal muscle  
insulin protease cleave insulin at similar sites.

AU Duckworth W C; Garcia J V; Liepnieks J J; Hamel F G; Hermodson M A;  
Frank

B H; Rosner M R

CS Veterans Administration Medical Center, Omaha, Nebraska.

NC CA35541 (NCI)

P60-AM-20542 (NIADDK)

SO BIOCHEMISTRY, (1989 Mar 21) 28 (6) 2471-7.

Journal code: 0370623. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198907

ED Entered STN: 19900309

Last Updated on STN: 19970203

Entered Medline: 19890727

L6 ANSWER 19 OF 32 MEDLINE

AN 89098952 MEDLINE

DN 89098952 PubMed ID: 2643113

TI A highly potent insulin: des-(B26-B30)-[AspB10,TyrB25-  
NH2]insulin(human).

AU Schwartz G P; Burke G T; Katsoyannis P G

CS Department of Biochemistry, Mount Sinai School of Medicine, City  
University of New York, NY 10029.

NC DK-12925 (NIDDK)

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF  
THE UNITED STATES OF

AMERICA, (1989 Jan) 86 (2) 458-61.

Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198902

ED Entered STN: 19900308

Last Updated on STN: 20000303

Entered Medline: 19890221

L6 ANSWER 20 OF 32 MEDLINE

AN 89088263 MEDLINE

DN 89088263 PubMed ID: 2642711

TI High resolution 1H-NMR studies of Des-(B26-B30)-insulin  
; assignment of resonances and properties of aromatic residues.

AU Hua Q X; Chen Y J; Wang C C; Wang D C; Roberts G C

CS Institute of Biophysics, Academia Sinica, Beijing, Peoples Republic of  
China.

NC DK-34035 (NIDDK)

SO BIOCHIMICA ET BIOPHYSICA ACTA, (1989 Feb 2) 994 (2) 114-20.

Journal code: 0217513. ISSN: 0006-3002.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198902

ED Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19890221

L6 ANSWER 21 OF 32 MEDLINE

AN 89064594 MEDLINE

DN 89064594 PubMed ID: 3058457

TI High performance liquid chromatographic analysis of insulin  
degradation products from a cultured kidney cell line.

AU Duckworth W C; Hamel F G; Liepnieks J; Frank B H; Yagil C; Rabkin R

CS Veterans Administration Medical Center, Omaha, Nebraska.

NC AM-32432 (NIADDK)

SO ENDOCRINOLOGY, (1988 Dec) 123 (6) 2701-8.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198901

ED Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19890117

L6 ANSWER 22 OF 32 MEDLINE

AN 88224894 MEDLINE

DN 88224894 PubMed ID: 2967179

TI Structural determinants of ligand recognition by type I insulin  
-like growth factor receptors: use of semisynthetic insulin  
analog probes.

AU Cara J F; Nakagawa S H; Tager H S

CS Department of Pediatrics, University of Chicago Pritzker School of  
Medicine, Illinois 60637.

NC DK-18347 (NIDDK)

DK-20595 (NIDDK)

SO ENDOCRINOLOGY, (1988 Jun) 122 (6) 2881-7.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198806

ED Entered STN: 19900308

Last Updated on STN: 20000303

Entered Medline: 19880628

L6 ANSWER 23 OF 32 MEDLINE

AN 88133996 MEDLINE

DN 88133996 PubMed ID: 3277618

TI Identification by fast atom bombardment mass spectrometry of  
insulin fragments produced by insulin proteinase.

AU Savoy L A; Jones R M; Pochon S; Davies J G; Muir A V; Offord R E;  
Rose K

CS Departement de Biochimie Medicale, Centre Medical Universitaire,  
Geneva,  
Switzerland.

SO BIOCHEMICAL JOURNAL, (1988 Jan 1) 249 (1) 215-22.

Journal code: 2984726R. ISSN: 0264-6021.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198803

ED Entered STN: 19900308

Last Updated on STN: 19900308

Entered Medline: 19880324

L6 ANSWER 24 OF 32 MEDLINE

AN 88112577 MEDLINE

DN 88112577 PubMed ID: 3322916

TI An examination of the role of insulin dimerisation and negative  
cooperativity using the biological properties of the despentapeptide and  
deshexapeptide insulins.

AU Cockram C S; Jones R H; Sonksen P H; Tatnell M A; Zhu S Q; Dodson G

CS Department of Medicine, St. Thomas' Hospital, London, UK.

SO DIABETOLOGIA, (1987 Sep) 30 (9) 733-8.

Journal code: 0006777. ISSN: 0012-186X.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198803

ED Entered STN: 19900305

Last Updated on STN: 20000303

Entered Medline: 19880307

L6 ANSWER 25 OF 32 MEDLINE

AN 87299010 MEDLINE

DN 87299010 PubMed ID: 3304338

TI Shortened insulin with enhanced in vitro potency.

AU Casaretto M; Spoden M; Diaconescu C; Gattner H G; Zahn H; Brandenburg D;

Wollmer A

SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1987 Jun) 368 (6) 709-16.

Journal code: 8503054. ISSN: 0177-3593.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198710

ED Entered STN: 19900305

Last Updated on STN: 19900305

Entered Medline: 19871006

L6 ANSWER 26 OF 32 MEDLINE

AN 87076065 MEDLINE

DN 87076065 PubMed ID: 3539147

TI Structure-function relationships of shortened [LeuB25]insulins, semisynthetic analogues of a mutant human insulin.

AU Fischer W H; Saunders D; Brandenburg D; Diaconescu C; Wollmer A; Dodson G;

De Meyts P; Zahn H

SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1986 Sep) 367 (9) 999-1006.

Journal code: 8503054. ISSN: 0177-3593.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198702

ED Entered STN: 19900302

Last Updated on STN: 19900302

Entered Medline: 19870204

L6 ANSWER 27 OF 32 MEDLINE

AN 86224000 MEDLINE

DN 86224000 PubMed ID: 3519607

TI Role of the phenylalanine B25 side chain in directing insulin interaction with its receptor. Steric and conformational effects.

AU Nakagawa S H; Tager H S

NC AM 18347 (NIADDK)

AM 20595 (NIADDK)

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1986 Jun 5) 261 (16) 7332-41.

Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198607

ED Entered STN: 19900321

Last Updated on STN: 20000303

Entered Medline: 19860702

L6 ANSWER 28 OF 32 MEDLINE

AN 85225974 MEDLINE

DN 85225974 PubMed ID: 3890892

TI A shortened insulin with full in vitro potency.

AU Fischer W H; Saunders D; Brandenburg D; Wollmer A; Zahn H

SO BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1985 May) 366 (5)

521-5.

Journal code: 8503054. ISSN: 0177-3593.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198508

ED Entered STN: 19900320

Last Updated on STN: 19900320

Entered Medline: 19850822

L6 ANSWER 29 OF 32 MEDLINE

AN 81013848 MEDLINE

DN 81013848 PubMed ID: 6997872

TI Semisynthesis and biological activity of porcine [LeuB24]insulin and [LeuB25]insulin.

AU Tager H; Thomas N; Assoian R; Rubenstein A; Saekow M; Olefsky J; Kaiser E

T

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF

AMERICA, (1980 Jun) 77 (6) 3181-5.

Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198011

ED Entered STN: 19900316

Last Updated on STN: 20000303

Entered Medline: 19801125

L6 ANSWER 30 OF 32 MEDLINE

AN 76141315 MEDLINE

DN 76141315 PubMed ID: 1254246

TI Further studies on the three-step-increase in activity due to the aromatic amino acids B24-26 (-Phe-Phe-Tyr-).

AU Weitzel G; Bauer F U; Eisele K

SO HOPPE-SEYLER'S ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1976 Feb) 357 (2) 187-200.

Journal code: 2985060R. ISSN: 0018-4888.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 197606

ED Entered STN: 19900313

Last Updated on STN: 19900313

Entered Medline: 19760602

L6 ANSWER 31 OF 32 MEDLINE

AN 76023789 MEDLINE

DN 76023789 PubMed ID: 1100508

TI B-chain shortening of matrix-bound insulin with pepsin, II. Preparation and properties of camel des-pentapeptide (B26-30)- and des-PheB1-des-pentapeptide (B26-30)- insulin.

AU Danho W O; Gattner H G; Nissen D; Zahn H

SO HOPPE-SEYLER'S ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1975 Sep) 356 (9) 1405-12.

Journal code: 2985060R. ISSN: 0018-4888.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 197601

ED Entered STN: 19900313

Last Updated on STN: 19900313

Entered Medline: 19760102

L6 ANSWER 32 OF 32 MEDLINE

AN 76023788 MEDLINE

DN 76023788 PubMed ID: 240771

TI [B-chain shortening of matrix-bound insulin by pepsin, I: Preparation and properties of bovine des-pentapeptide (B26-30) insulin (author's transl)].  
B-Kettenverkürzung von polymergebundenem Insulin mit Pepsin, I.

Darstellung und Eigenschaften von Des-Pentapeptid (B26-30)-Rinderinsulin.  
 AU Gattner H G  
 SO HOPPE-SEYLER'S ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1975 Sep) 356 (9) 1397-404.  
 Journal code: 2985060R. ISSN: 0018-4888.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA German  
 FS Priority Journals  
 EM 197601  
 ED Entered STN: 19900313  
 Last Updated on STN: 19950206  
 Entered Medline: 19760102

=> d 27 abs

L8 HAS NO ANSWERS

L1 195067 SEA FILE=MEDLINE INSULIN  
 L5 87 SEA FILE=MEDLINE L1 AND B25  
 L6 32 SEA FILE=MEDLINE L5 AND B26  
 L8 0 SEA FILE=MEDLINE L6 AND B28

=> s 16

137 B26  
 L9 32 L5 AND B26

=> d 27 abs

L9 ANSWER 27 OF 32 MEDLINE

AB To gain an understanding of the causes of decreased biological activity in insulins bearing amino acid substitutions at position B25 and the importance of the PheB25 side chain in directing hormone-receptor interactions, we have prepared a variety of insulin analogs and have studied both their interactions with isolated canine hepatocytes and their abilities to stimulate glucose oxidation by isolated rat adipocytes. The semisynthetic analogs fall into three structural classes: (a) analogs in which the COOH-terminal 5, 6, or 7 residues of the insulin B-chain have been deleted, but in which the COOH-terminal residue of the B-chain has been derivatized by alpha-carboxamidation; (b) analogs in which PheB25 has been replaced by unnatural aromatic or natural L-amino acids; and (c) analogs in which the COOH-terminal 5 residues of the insulin B-chain have been deleted and in which residue B25 has been replaced by selected alpha-carboxamidated amino acids. Our results showed that (a) insulin residues B26-B30 can be deleted without decrease in biological potency, whereas deletion of residues B25-B30 and B24-B30 causes a marked and cumulative decrease in potency; (b) replacement of PheB25 in insulin by Leu or Ser results in analogs with biological potency even less than that observed when residues B25-B30 are deleted; (c) the side chain bulk of naphthyl(1)-alanine or naphthyl(2)-alanine at position B25 is well tolerated during insulin interactions with receptor, whereas that of homophenylalanine is not; and (d) the decreased biological potency attending substitution of insulin PheB25 by Ala, Ser, Leu, or homophenylalanine is reversed, in part or in total, by deletion of COOH-terminal residues B26-B30. Additional experiments showed that the rate of dissociation of receptor-bound <sup>125</sup>I-labeled insulin from isolated hepatocytes is enhanced by incubating cells with insulin or [naphthyl(2)-alanineB25]insulin, but not with analogs in which PheB25 is replaced by serine, leucine, or homophenylalanine; deletion of residues B26-B30, however, results in analogs that enhance the rate of dissociation of receptor-bound insulin in all cases studied. We conclude that (a) steric hindrance involving the COOH-terminal domain of the B chain plays a major role in directing the interaction of insulin with its receptor; (b) the initial negative effect of this domain is reversed upon the filling of a site reflecting interaction of the receptor and the beta-aromatic ring of the PheB25 side chain.(ABSTRACT TRUNCATED

AT 400  
 WORDS)

=> d 17 abs

L9 ANSWER 17 OF 32 MEDLINE

AB Despentapeptide (B26-30)-insulinamide (B25) prepared

by a semisynthetic procedure was found to have about 65% of the hypoglycaemic activity of natural insulin. In contrast, the binding of the modified insulin analogue to insulin specific receptors was markedly increased. The discrepancy between the loss of biological potency and the apparent increase in binding affinity for membrane receptors reveals that not all of the biological activity of insulin is regulated by the receptor-binding system. The tetrapeptidamide of the B-chain of insulin (Arg-Gly-Phe-Phe-NH<sub>2</sub>) was clearly shown to have both insulin-like and insulin -potentiating actions in vivo although it had no effect on insulin receptor function in vitro. Evidence suggests that the small peptide fragment of insulin may be internalized and acts at the post-binding site(s) of the glucose metabolic pathway in target tissues. The present data support the general concept that insulin may exert its complex molecular actions through internalized hormonal fragment as well as the transmembrane mediators generated from receptor binding.

=> d 13 abs

L9 ANSWER 13 OF 32 MEDLINE

AB By use of isolated canine hepatocytes and insulin analogs prepared by trypsin-catalyzed semisynthesis, we have investigated the importance of the aromatic triplet PheB24-PheB25-TyrB26 of the COOH-terminal B-chain domain of insulin in directing the affinity of insulin-receptor interactions. Analysis of the receptor binding potencies of analogs bearing transpositions or replacements (by Tyr, D-Tyr or their corresponding 3,5-diiodo derivatives) in this region demonstrates a wide divergence in the acceptance both of configurational change (with [D-TyrB24,PheB26]insulin and [D-TyrB25,PheB26]insulin exhibiting 160 and 0.1% of the receptor binding potency of insulin, respectively) and of detailed side chain structure (with [TyrB24,PheB26]insulin and [TyrB25,PheB26]insulin exhibiting 2 and 80% of the receptor binding potency of insulin, respectively). Additional experiments addressed the solvent accessibilities of the 4 tyrosine residues of insulin and the insulin analogs at selected peptide concentrations by use of analytical radioiodination. Whereas two analogs ([TyrB25,PheB26]insulin and [D-TyrB24,PheB26]insulin) were found to undergo self aggregation, no strict correlation was found between the ability of an analog to aggregate and its potency for interaction with the insulin receptor. Related findings are discussed in terms of the interplay between side chain and main chain structure in the COOH-terminal domain of the insulin B-chain and the structural attributes of insulin that determine the affinity of insulin-receptor interactions.

=> d his

(FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002)

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

L1 195067 S INSULIN  
 L2 2 S L1 AND A16 AND A17  
 L3 153 S L1 AND B7  
 L4 15 S L3 AND A7  
 L5 87 S L1 AND B25  
 L6 32 S L5 AND B26  
 L7 1 S L6 AND B27  
 L8 0 S L6 AND B28  
 L9 32 S L6

=> s 11 and b14

374 B14  
 L10 17 L1 AND B14

=> d 1-17

L10 ANSWER 1 OF 17 MEDLINE

AN 2000417572 MEDLINE  
 DN 20393861 PubMed ID: 10933788  
 TI The receptor binding conformation of bombyxin is induced by alanine(B15).  
 AU Fullbright G; Bullesbach E E  
 CS Department of Biochemistry and Molecular Biology, Medical University of South Carolina, 173 Ashley Avenue, P.O. Box 250509, Charleston, South Carolina 29425, USA.  
 SO BIOCHEMISTRY, (2000 Aug 15) 39 (32) 9718-24.

Journal code: 0370623. ISSN: 0006-2960.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200009  
ED Entered STN: 20000915  
Last Updated on STN: 20000915  
Entered Medline: 20000905

L10 ANSWER 2 OF 17 MEDLINE  
AN 97348311 MEDLINE  
DN 97348311 PubMed ID: 9204362  
TI Purification and structural characterization of insulin from the lesser siren, *Siren intermedia* (Amphibia: Caudata).  
AU Conlon J M; Trauth S E; Sever D M  
CS Department of Biomedical Sciences, Creighton University Medical School, Omaha, Nebraska 68178, USA.  
SO GENERAL AND COMPARATIVE ENDOCRINOLOGY, (1997 Jun) 106 (3) 295-300.  
Journal code: 0370735. ISSN: 0016-6480.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199708  
ED Entered STN: 19970908  
Last Updated on STN: 19970908  
Entered Medline: 19970826

L10 ANSWER 3 OF 17 MEDLINE  
AN 97290728 MEDLINE  
DN 97290728 PubMed ID: 9145374  
TI Toward understanding insulin fibrillation.  
AU Brange J; Andersen L; Laursen E D; Meyn G; Rasmussen E  
CS Novo Nordisk A/S, Novo Alle, Bagsvaerd, Denmark.  
SO JOURNAL OF PHARMACEUTICAL SCIENCES, (1997 May) 86 (5) 517-25. Ref: 78  
Journal code: 2985195R. ISSN: 0022-3549.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199708  
ED Entered STN: 19970813  
Last Updated on STN: 19970813  
Entered Medline: 19970807

L10 ANSWER 4 OF 17 MEDLINE  
AN 97251323 MEDLINE  
DN 97251323 PubMed ID: 9097005  
TI IDDM in an adolescent patient with common variable immunodeficiency.  
CM Comment in: Diabetes Care. 1998 Jun;21(6):1029  
AU Metin A; Tezcan I; Ozyurek H  
SO DIABETES CARE, (1997 Apr) 20 (4) 677-8.  
Journal code: 7805975. ISSN: 0149-5992.  
CY United States  
DT Letter  
LA English  
FS Priority Journals; AIDS  
EM 199706  
ED Entered STN: 19970620  
Last Updated on STN: 19990129  
Entered Medline: 19970609

L10 ANSWER 5 OF 17 MEDLINE  
AN 97157004 MEDLINE  
DN 97157004 PubMed ID: 9003385  
TI The characterization of endosomal insulin degradation intermediates and their sequence of production.  
AU Seabright P J; Smith G D  
CS University of Cambridge, Department of Clinical Biochemistry, Addenbrooke's Hospital, U.K.  
SO BIOCHEMICAL JOURNAL, (1996 Dec 15) 320 ( Pt 3) 947-56.  
Journal code: 2984726R. ISSN: 0264-6021.  
CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199702  
ED Entered STN: 19970305  
Last Updated on STN: 20000303  
Entered Medline: 19970214

L10 ANSWER 6 OF 17 MEDLINE  
AN 95144310 MEDLINE  
DN 95144310 PubMed ID: 7842106  
TI [Turner syndrome and insulin-dependent diabetes mellitus].  
Syndrome de Turner et diabete insulinodependant.  
AU Franzese A; De Filippo G; Argenziano A; Salerno M C  
CS Departement de pediatrie, universite de Naples Federico II, Italie.  
SO ARCHIVES DE PEDIATRIE, (1994 Aug) 1 (8) 727-9.  
Journal code: 9421356. ISSN: 0929-693X.  
CY France  
DT Journal; Article; (JOURNAL ARTICLE)  
LA French  
FS Priority Journals  
EM 199503  
ED Entered STN: 19950316  
Last Updated on STN: 19950316  
Entered Medline: 19950309

L10 ANSWER 7 OF 17 MEDLINE  
AN 94224857 MEDLINE  
DN 94224857 PubMed ID: 8171015  
TI Naturally processed heterodimeric disulfide-linked insulin peptides bind to major histocompatibility class II molecules on thymic epithelial cells.  
AU Forquet F; Hadzija M; Semple J W; Speck E; Delovitch T L  
CS Banting and Best Department of Medical Research, University of Toronto, ON, Canada.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Apr 26) 91 (9) 3936-40.  
Journal code: 7505876. ISSN: 0027-8424.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199406  
ED Entered STN: 19940613  
Last Updated on STN: 19940613  
Entered Medline: 19940601

L10 ANSWER 8 OF 17 MEDLINE  
AN 90062153 MEDLINE  
DN 90062153 PubMed ID: 2684974  
TI Identification of insulin intermediates and sites of cleavage of native insulin by insulin protease from human fibroblasts.  
AU Stentz F B; Kitabchi A E; Schilling J W; Schronk L R; Seyer J M  
CS Department of Medicine and Clinical Research Center, University of Tennessee, Memphis 38163.  
NC RR00211 (NCRR)  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1989 Dec 5) 264 (34) 20275-82.  
Journal code: 2985121R. ISSN: 0021-9258.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199001  
ED Entered STN: 19900328  
Last Updated on STN: 19970203  
Entered Medline: 19900108

L10 ANSWER 9 OF 17 MEDLINE  
AN 89274174 MEDLINE  
DN 89274174 PubMed ID: 2659071  
TI Drosophila insulin degrading enzyme and rat skeletal muscle insulin protease cleave insulin at similar sites.  
AU Duckworth W C; Garcia J V; Liepnieks J J; Hamel F G; Hermodson M A; Frank  
B H; Rosner M R

CS Veterans Administration Medical Center, Omaha, Nebraska.  
NC CA35541 (NCI)

P60-AM-20542 (NIADDK)

SO BIOCHEMISTRY, (1989 Mar 21) 28 (6) 2471-7.

Journal code: 0370623. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198907

ED Entered STN: 19900309

Last Updated on STN: 19970203

Entered Medline: 19890727

L10 ANSWER 10 OF 17 MEDLINE

AN 89064594 MEDLINE

DN 89064594 PubMed ID: 3058457

TI High performance liquid chromatographic analysis of insulin degradation products from a cultured kidney cell line.

AU Duckworth W C; Hamel F G; Liepnieks J; Frank B H; Yagil C; Rabkin R

CS Veterans Administration Medical Center, Omaha, Nebraska.

NC AM-32432 (NIADDK)

SO ENDOCRINOLOGY, (1988 Dec) 123 (6) 2701-8.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198901

ED Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19890117

L10 ANSWER 11 OF 17 MEDLINE

AN 88133996 MEDLINE

DN 88133996 PubMed ID: 3277618

TI Identification by fast atom bombardment mass spectrometry of insulin fragments produced by insulin proteinase.

AU Savoy L A; Jones R M; Pochon S; Davies J G; Muir A V; Offord R E; Rose K

CS Departement de Biochimie Medicale, Centre Medical Universitaire, Geneva, Switzerland.

SO BIOCHEMICAL JOURNAL, (1988 Jan 1) 249 (1) 215-22.

Journal code: 2984726R. ISSN: 0264-6021.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198803

ED Entered STN: 19900308

Last Updated on STN: 19900308

Entered Medline: 19880324

L10 ANSWER 12 OF 17 MEDLINE

AN 86018543 MEDLINE

DN 86018543 PubMed ID: 4048801

TI Testing histocompatibility antigens (loci A and B) in a group of type 1 (insulin-dependent) diabetic patients in Bucharest.

AU Mincu I; Cheta D; Truia C I; Truia M; Ionescu-Tirgoviste C; Ilinca D

SO MEDECINE INTERNE, (1985 Jul-Sep) 23 (3) 207-11.

Journal code: 7506353. ISSN: 0377-1202.

CY Romania

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198511

ED Entered STN: 19900321

Last Updated on STN: 19900321

Entered Medline: 19851112

L10 ANSWER 13 OF 17 MEDLINE

AN 83286008 MEDLINE

DN 83286008 PubMed ID: 6411398

TI Population genetic analyses of insulin dependent diabetes mellitus using HLA allele frequencies.

AU Murphy C C; Acton R T; Barger B O; Go R C; Kirk K A; Reitnauer P J; Roseman J M

SO CLINICAL GENETICS, (1983 Jun) 23 (6) 405-14.

Journal code: 0253664. ISSN: 0009-9163.

CY Denmark

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198310

ED Entered STN: 19900319

Last Updated on STN: 19900319

Entered Medline: 19831021

L10 ANSWER 14 OF 17 MEDLINE

AN 82182778 MEDLINE

DN 82182778 PubMed ID: 7074001

TI Analysis of HLA antigen association with proliferative diabetic retinopathy.

AU Johnston P B; Kidd M; Middleton D; Greenfield A A; Archer D B; Maguire C

J; Kennedy L

SO BRITISH JOURNAL OF OPHTHALMOLOGY, (1982 May) 66 (5) 277-9.

Journal code: 0421041. ISSN: 0007-1161.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198207

ED Entered STN: 19900317

Last Updated on STN: 19900317

Entered Medline: 19820719

L10 ANSWER 15 OF 17 MEDLINE

AN 82113731 MEDLINE

DN 82113731 PubMed ID: 7034782

TI Initial sites of insulin cleavage and stereospecificity of carboxyl proteinases from *Aspergillus sojae* and *Pycnoporus coccineus*.

AU Ichishima E; Emi M; Majima E; Mayumi Y; Kumagai H; Hayashi K; Tomoda K

SO BIOCHIMICA ET BIOPHYSICA ACTA, (1982 Jan 18) 700 (2) 247-53.

Journal code: 0217513. ISSN: 0006-3002.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198204

ED Entered STN: 19900317

Last Updated on STN: 20000303

Entered Medline: 19820412

L10 ANSWER 16 OF 17 MEDLINE

AN 82085363 MEDLINE

DN 82085363 PubMed ID: 6947506

TI HLA associations with insulin-dependent diabetes mellitus in a sample of the American Black population.

AU Reitnauer P J; Roseman J M; Barger B O; Murphy C C; Kirk K A; Acton R T

SO TISSUE ANTIGENS, (1981 Mar) 17 (3) 286-93.

Journal code: 0331072. ISSN: 0001-2815.

CY Denmark

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198202

ED Entered STN: 19900316

Last Updated on STN: 19900316

Entered Medline: 19820222

L10 ANSWER 17 OF 17 MEDLINE

AN 81024848 MEDLINE

DN 81024848 PubMed ID: 7418963

TI HLA and insulin-dependent diabetes in South African negroes.

AU Hammond M G; Asmal A C; Omar M A

SO DIABETOLOGIA, (1980 Aug) 19 (2) 101-2.

Journal code: 0006777. ISSN: 0012-186X.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198012  
ED Entered STN: 19900316  
Last Updated on STN: 19900316  
Entered Medline: 19801218

=> d 8 abs

L10 ANSWER 8 OF 17 MEDLINE

AB We have studied the time sequence degradation of native insulin by insulin protease from human fibroblast using multiple steps involving purification of the products by high performance liquid chromatography, determination of peak composition by amino acid sequence analysis, and confirmation of structure by mass spectrometry and thus elucidated the sites of cleavage of insulin by human insulin protease. We observed that as early as 0.5 min of incubation, three major new peptide peaks, intact insulin, and four smaller peptide peaks can be detected. The major peptides are portions of the insulin molecule, with the amino ends of the A and B chains or the carboxyl ends of the A and B chains still connected by disulfide bonds. Peptide peak I is A1-13-B1-9. Peptide peak II is A1-14-B1-9. Peptide peak III is A14-21-B14-30. The smaller peptide peaks are A14-21-B17-30, A15-21-B14-30, A15-21-B10-30, and A14-21-B10-30. The major peptide bond cleavage sites therefore consist of A13-14, A14-15, B9-10, B13-14, and B10-17. With longer incubation times, peptide peak II appears to lose the A14 tyrosine to form peptide peak I. This peptide I, which is the amino end of the A and B chains, is not further degraded even after 1.5 h of incubation. With longer incubation times, the peptides containing the carboxyl ends of the A and B chains are further degraded to form products from cleavage at the A18-19, B14-15, B25-26, and a small amount of A19-20, B10-11, and B24-25 cleavage and the emergence of 2-5-amino acid peptide chains, tyrosine, alanine, histidine, and leucine-tyrosine. We conclude, based on the three-dimensional structure of insulin, that human insulin protease recognizes the alpha-helical regions around leucine-tyrosine bonds and that final degradation steps to small peptides do not require lysosomal involvement.

=> d his

(FILE 'HOME' ENTERED AT 10:42:37 ON 20 DEC 2002)

FILE 'MEDLINE' ENTERED AT 10:42:43 ON 20 DEC 2002

L1 195067 S INSULIN  
L2 2 S L1 AND A16 AND A17  
L3 153 S L1 AND B7  
L4 15 S L3 AND A7  
L5 87 S L1 AND B25  
L6 32 S L5 AND B26  
L7 1 S L6 AND B27  
L8 0 S L6 AND B28  
L9 32 S L6  
L10 17 S L1 AND B14

=> s l1 and B8

2230 B8

L11 279 L1 AND B8

=> s l11 and b12

9166 B12

L12 14 L11 AND B12

=> d 1-14

L12 ANSWER 1 OF 14 MEDLINE

AN 97294699 MEDLINE

DN 97294699 PubMed ID: 9148904

TI Alanine scanning mutagenesis of insulin.

AU Kristensen C; Kjeldsen T; Wiberg F C; Schaffer L; Hach M; Havelund S; Bass

J; Steiner D F; Andersen A S

CS Department of Insulin Research, Novo Nordisk, 2880 Bagsvaerd, Denmark.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 16) 272 (20) 12978-83.

Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199706

ED Entered STN: 19970630

Last Updated on STN: 19970630

Entered Medline: 19970619

L12 ANSWER 2 OF 14 MEDLINE

AN 94372913 MEDLINE

DN 94372913 PubMed ID: 6153043

TI Histocompatibility antigens and insulin-dependent diabetes: a study of 20 Brazilian families.

AU Gomes M B; Ruzany F; Quadra A A; Sarno E N; Arduino F

CS Departamento de Patologia, Faculdade de Ciencias Medicas, Universidade do

Estado do Rio de Janeiro, Brasil.

SO BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, (1981 Dec) 14 (6) 379-81.

Journal code: 8112917. ISSN: 0100-879X.

CY Brazil

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199410

ED Entered STN: 19941031

Last Updated on STN: 19941031

Entered Medline: 19941019

L12 ANSWER 3 OF 14 MEDLINE

AN 94336586 MEDLINE

DN 94336586 PubMed ID: 8058669

TI [Immunologic characterization of patients with insulin-dependent diabetes mellitus with varying duration of disease].

Immunologicheskoe kharakteristiki bol'nykh insulinzavisimym sakharnym diabetom s razlichnoi dlitel'nost'iu zavolevaniia.

AU Shishko P I; Dreval' A V; Sadykova R E; Efuni S S; Matiukov A e; Abugova I

A; Polianskaia I S; Skuibin B G; Filatov A V

SO PROBLEMY ENDOKRINOLOGII, (1993 Jan-Feb) 39 (1) 8-11.

Journal code: 0140673. ISSN: 0375-9660.

CY RUSSIA: Russian Federation

DT Journal; Article; (JOURNAL ARTICLE)

LA Russian

FS Priority Journals

EM 199409

ED Entered STN: 19940920

Last Updated on STN: 19940920

Entered Medline: 19940913

L12 ANSWER 4 OF 14 MEDLINE

AN 92193228 MEDLINE

DN 92193228 PubMed ID: 1724775

TI Human leucocyte antigen and insulin dependent diabetes mellitus.

AU Gupta M M; Raghunath D; Kher S K; Radhakrishnan A P

CS Department of Medicine, Armed Forces Medical College, Pune.

SO JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA, (1991 Jul) 39 (7) 540-3.

Journal code: 7505585. ISSN: 0004-5772.

CY India

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199204

ED Entered STN: 19920509

Last Updated on STN: 19960129

Entered Medline: 19920423

L12 ANSWER 5 OF 14 MEDLINE

AN 92113037 MEDLINE

DN 92113037 PubMed ID: 1730786

TI Effects of growth factors, hormones, bacterial lipopolysaccharides, and lipotechoic acids on the clonal growth of normal ureteral epithelial cells in serum-free culture.

AU Wille J J; Park J; Elgavish A

CS Southern Research Institute, Birmingham, Alabama 35255.

NC DK39852 (NIDDK)  
 SO JOURNAL OF CELLULAR PHYSIOLOGY, (1992 Jan) 150 (1) 52-8.  
 Journal code: 0050222. ISSN: 0021-9541.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199202  
 ED Entered STN: 19920308  
 Last Updated on STN: 19920308  
 Entered Medline: 19920218

L12 ANSWER 6 OF 14 MEDLINE  
 AN 86185180 MEDLINE  
 DN 86185180 PubMed ID: 6443704  
 TI [HLA typing and insulin antibody production in insulin  
 -dependent diabetics].  
 Tipizzazione HLA e produzione di anticorpi anti-insulina nel diabetico  
 insulina-dipendente.  
 AU Bruni B; Barolo P; Gadaleta G; Gamba Ansaldi S; Grassi G; Zerbinati A;  
 Molinatti M; Salvetti E  
 SO ANNALI DELL'OSPEDALE MARIA VITTORIA DI TORINO, (1984  
 Jul-Dec) 27 (7-12)  
 185-213.  
 Journal code: 7511607. ISSN: 0390-5454.  
 CY Italy  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA Italian  
 FS Priority Journals  
 EM 198605  
 ED Entered STN: 19900321  
 Last Updated on STN: 19900321  
 Entered Medline: 19860521

L12 ANSWER 7 OF 14 MEDLINE  
 AN 86018543 MEDLINE  
 DN 86018543 PubMed ID: 4048801  
 TI Testing histocompatibility antigens (loci A and B) in a group of type 1 (insulin-dependent) diabetic patients in Bucharest.  
 AU Mincu I; Cheta D; Truia C I; Truia M; Ionescu-Tirgoviste C; Ilinca D  
 SO MEDECINE INTERNE, (1985 Jul-Sep) 23 (3) 207-11.  
 Journal code: 7506353. ISSN: 0377-1202.  
 CY Romania  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198511  
 ED Entered STN: 19900321  
 Last Updated on STN: 19900321  
 Entered Medline: 19851112

L12 ANSWER 8 OF 14 MEDLINE  
 AN 85091506 MEDLINE  
 DN 85091506 PubMed ID: 3880963  
 TI Recurrence of diabetic nodular glomerulosclerosis in a renal transplant.  
 AU Maryniak R K; Mendoza N; Clyne D; Balakrishnan K; Weiss M A  
 SO TRANSPLANTATION, (1985 Jan) 39 (1) 35-8.  
 Journal code: 0132144. ISSN: 0041-1337.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198502  
 ED Entered STN: 19900320  
 Last Updated on STN: 19900320  
 Entered Medline: 19850213

L12 ANSWER 9 OF 14 MEDLINE  
 AN 84100481 MEDLINE  
 DN 84100481 PubMed ID: 6581663  
 TI Increased frequency of HLA-Cw4 in type 2 diabetes.  
 AU Groop L; Koskimies S; Pelkonen R; Tolppanen E M  
 SO ACTA ENDOCRINOLOGICA, (1983 Dec) 104 (4) 475-8.  
 Journal code: 0370312. ISSN: 0001-5598.  
 CY Denmark  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals

EM 198402  
 ED Entered STN: 19900319  
 Last Updated on STN: 19900319  
 Entered Medline: 19840214

L12 ANSWER 10 OF 14 MEDLINE  
 AN 82096724 MEDLINE  
 DN 82096724 PubMed ID: 6947952  
 TI Is diabetic microangiopathy genetically heterogeneous? HLA and diabetic nephropathy.  
 AU Barbosa J  
 NC AM20729 (NIADDK)  
 NO1-HD-8-2846 (NICHHD)  
 RR-400 (NCRR)  
 SO HORMONE AND METABOLIC RESEARCH. SUPPLEMENT, (1981)  
 11 77-80.  
 Journal code: 0330417. ISSN: 0170-5903.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198203  
 ED Entered STN: 19900317  
 Last Updated on STN: 19970203  
 Entered Medline: 19820313

L12 ANSWER 11 OF 14 MEDLINE  
 AN 81036974 MEDLINE  
 DN 81036974 PubMed ID: 6158864  
 TI Histocompatibility antigen frequencies in diabetic retinopathy.  
 AU Barbosa J; Ramsay R C; Knobloch W H; Cantrill H L; Noreen H; King R; Yunis E  
 NC 1 R01 AM20729 (NIADDK)  
 1 R01 EY02445 (NEI)  
 NO1-HD-8-2846 (NICHHD)  
 SO AMERICAN JOURNAL OF OPHTHALMOLOGY, (1980 Aug) 90 (2)  
 148-53.  
 Journal code: 0370500. ISSN: 0002-9394.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 198012  
 ED Entered STN: 19900316  
 Last Updated on STN: 19970203  
 Entered Medline: 19801218

L12 ANSWER 12 OF 14 MEDLINE  
 AN 79092609 MEDLINE  
 DN 79092609 PubMed ID: 732354  
 TI HLA antigens in patients with juvenile diabetes and their first-degree relatives.  
 AU Krawisz J E; Palumbo P J; Taswell H F; Elveback L R  
 SO MAYO CLINIC PROCEEDINGS, (1978 Dec) 53 (12) 782-7.  
 Journal code: 0405543. ISSN: 0025-6196.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 197903  
 ED Entered STN: 19900315  
 Last Updated on STN: 19900315  
 Entered Medline: 19790313

L12 ANSWER 13 OF 14 MEDLINE  
 AN 77225936 MEDLINE  
 DN 77225936 PubMed ID: 885296  
 TI HLA antigens in Japanese patients with diabetes mellitus.  
 AU Nakao Y; Fukunishi T; Koide M; Akasawa K; Ikeda M  
 SO DIABETES, (1977 Aug) 26 (8) 736-9.  
 Journal code: 0372763. ISSN: 0012-1797.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 197709  
 ED Entered STN: 19900314

Last Updated on STN: 19900314  
Entered Medline: 19770929

L12 ANSWER 14 OF 14 MEDLINE

AN 76243985 MEDLINE

DN 76243985 PubMed ID: 133329

TI [HL-A antigens in insulin-dependent diabetes mellitus]].

Antigenes HLA chez les diabetiques insulino-dependants.

AU Mirouze J; Seignalet J; Selam J L; Lapinski H; Jaffiol C

SO NOUVELLE PRESSE MEDICALE, (1976 Jun 26) 5 (26) 1628-30.

Journal code: 0312552. ISSN: 0301-1518.

CY France

DT Journal; Article; (JOURNAL ARTICLE)

LA French

FS Priority Journals

EM 197609

ED Entered STN: 19900313

Last Updated on STN: 19900313

Entered Medline: 19760925

=> d l abs

L12 ANSWER 1 OF 14 MEDLINE

AB Alanine scanning mutagenesis has been used to identify specific side chains of insulin which strongly influence binding to the insulin receptor. A total of 21 new insulin analog constructs were made, and in addition 7 high pressure liquid chromatography-purified analogs were tested, covering alanine substitutions in positions B1, B2, B3, B4, B8, B9, B10, B11, B12, B13, B16, B17, B18, B20, B21, B22, B26, A4, A8, A9, A12, A13, A14, A15, A16, A17, A19, and A21. Binding data on the analogs revealed that the alanine mutations that were most disruptive for binding were at positions TyrA19, GlyB8, LeuB11, and GluB13, resulting in decreases in affinity of 1,000-, 33-, 14-, and 8-fold, respectively, relative to wild-type insulin. In contrast, alanine substitutions at positions GlyB20, ArgB22, and SerA9 resulted in an increase in affinity for the insulin receptor. The most striking finding is that B20Ala insulin retains high affinity binding to the receptor. GlyB20 is conserved in insulins from different species, and in the structure of the B-chain it appears to be essential for the shift from the alpha-helix B8-B19 to the beta-turn B20-B22. Thus, replacing GlyB20 with alanine most likely modifies the structure of the B-chain in this region, but this structural change appears to enhance binding to the insulin receptor.